Considerations and challenges associated with developing Phase-Appropriate Stability programs for Investigational Medicinal Products

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Agenda

- General overview of stability
- Drug development process & phases of clinical research
- Considerations for stability in early phase work

The purpose of stability testing……

- To provide evidence on how the quality of a DS or DP varies with time under the influence of a variety of environmental conditions like temperature, humidity and light.

- To establish a shelf life for the DP

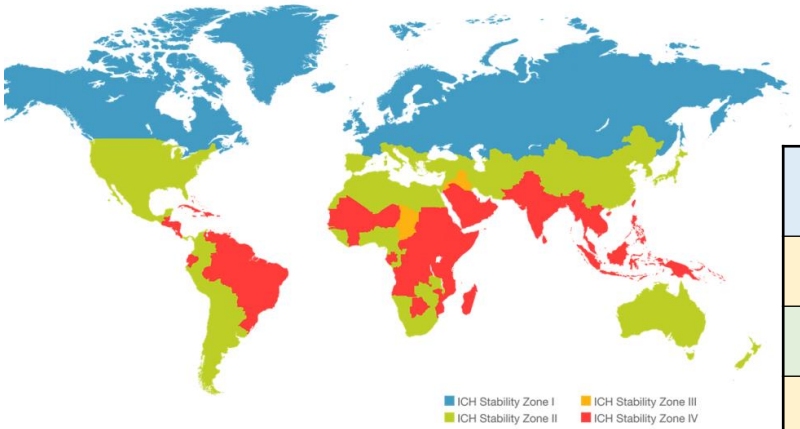
- Determine the most suitable storage conditions

- ICH Q1A(R2): Stability testing of new drug substances and products

Types of Stability

- **Chemical** – The DP or DS retains its chemical integrity and strength, within the specified limits or specifications.
- **Physical** – The original physical properties, including appearance, colour, odour, melting point, uniformity of dissolution, viscosity, etc are retained.
- **Microbial** – antimicrobial effectiveness, sterility or resistance to microbial growth is retained within the specified limits.
- **Therapeutic** – the therapeutic effect remains unchanged.
- **Toxicological** – No significant increase in toxicity occurs.

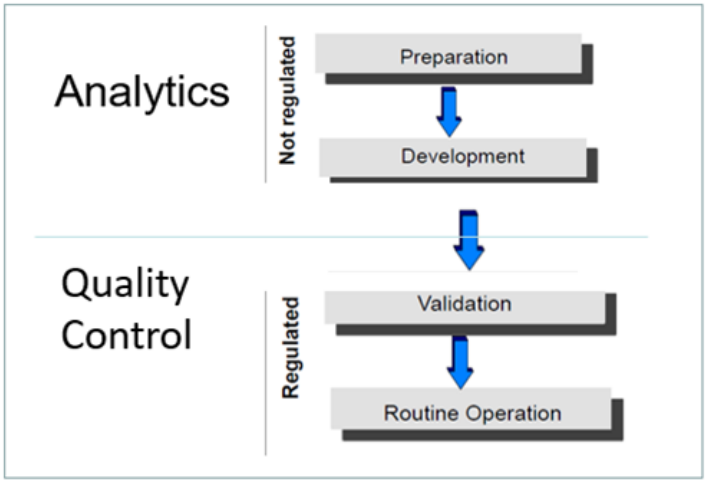
How do we do that? Storage



Climatic Zone	Type of Climate	Recommended Conditions
Zone I	Temperate	21°C/45%RH
Zone II	Mediterranean/Subtropical	25°C/60%RH
Zone III	Hot, Dry	30°C/35%RH
Zone IVa	Hot Humid/ Tropical	30°C/65%RH
Zone IVb	Hot/ Higher Humidity	30°C/75%RH

How do we do that? QC Testing

Physio-chemical Properties
pH (potentiometry)
Intact MW (SEC, CE, SDS-PAGE)
Osmolality (Freezing Point Depression)
Concentration (A280, SoloVPE)
Potency (SPR, ELISA)
Identity (project Specific)
Appearance (visual inspection)
Product Purity (HPLC, CE, SDS-PAGE
Potency (ELISA)
Bespoke Stability programs



Product-related Impurities
Aggregates (SEC-HPLC, DLS, MS)
Charge variants (IEF, CE, HPLC)
Breakdown (SDS-PAGE, CE)
Hydrophobic profiles (RP & HIC)
Impurity Identification

Safety
Endotoxin
Mycoplasma
Bioburden
Particulate matter

Process-related Impurities
Host Cell Proteins (ELISA)
Host Cell DNA (qPCR)
Residual Protein A (ELISA)

Performance Parameter	Assay	Impurities		Identification
		Quantitative	Limit Test	
Accuracy	Yes	Yes	No	No
Precision-repeatability	Yes	Yes	No	No
Precision-intermediate	Yes	Yes	No	No
Linearity	Yes	Yes	No	No
Range	Yes	Yes	No	No
Specificity	Yes	Yes	Yes	Yes
Detection Limit	No	May be required	Yes	No
Quantitation Limit	No	Yes	No	No

What does it look like? ICH Guidelines

Q1A - Q1F Stability	
Q1A(R2)	Stability Testing of New Drug Substances and Products
Q1B	Stability Testing : Photostability Testing of New Drug Substances and Products
Q1C	Stability Testing for New Dosage Forms
Q1D	Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products
Q1E	Evaluation of Stability Data
Q1F	Stability Data Package for Registration Applications in Climatic Zones III and IV
Q1/Q5C EWG	Targeted Revisions of the ICH Stability Guideline Series

What does it look like?

	TEST METHOD	ACCEPTANCE CRITERIA	TIME POINT (MONTHS)[1]				
			0[2]	3	6	9[3]	12[3]
Characteristics	Appearance (visual) USP <631>	Clear to opalescent. Colorless to slightly brown/yellow liquid.	x	AB	A	A	A
	Particles (visual) USP <790>	Report result	x	AB	A	A	A
	Subvisible Particles USP <787>	Report results for ≥ 10 µm and ≥ 25 µm pt/vial	x	NT	NT	NT	A
	pH (Potentiometry) USP <791>	7.30 ± 0.30	x	AB	A	A	A
	Protein concentration (A_{280})	7.0 ± 0.5 mg/mL	x	AB	A	A	A
	DAR	0.8 – 2.0	x	AB	A	A	A
Identity	cIEF	Comparable to reference Report pI and % peak area main peak Report % peak areas of acidic peaks Report % peak areas of acidic peaks	x	AB	A	A	A
Purity	SE-HPLC	Monomer: ≥ 95 %, HMWS: ≤ 5%, LMWS: report	x	AB	A	A	A
	CE-SDS reducing	Comparable to reference ≥ 90 % heavy and light chain	x	AB	A	A	A
	CE-SDS non-reducing	Comparable to reference ≥ 90 % Intact mAb	x	AB	A	A	A
Potency	Affinity ELISA	3.5 – 14 ng/mL	x	AB	A	A	A
Safety	Bioburden	≤ 1 cfu / 10 mL	x	NT	NT	NT	A

[1] A = stored frozen at ≤ -65 °C; B = stored at 2 – 8 °C; NT = Not tested.
[2] Samples tested as part of batch release.

Phases of Drug Development

Phase	Purpose	Participants
Preclinical/Tox	safety biological activity formulation	Animal Studies
Phase I	safety dosage	20-100 healthy volunteers
Phase II	determine effectiveness look for side effects	100-500 patient volunteers
Phase III	confirm effectiveness monitor adverse reactions from sustained use	1000-5000 patient volunteers
Phase IV	post-market monitoring and testing	

- All stages of the drug development life cycle involve CMC (Chemistry, Manufacturing, and Controls).

- The stability programs during the drug development process are critical to ensuring safety, efficacy, and quality.

Phase Appropriate Stability

GMP requirements apply for Phase I. However, GMP has different meanings for Phase I investigational products than for commercially available drugs. This is sometimes confused with Phase I drugs being “exempt” from GMP guidelines, but it’s more accurate to describe Phase I materials as exempt from certain GMP requirements.

Stability is a critical quality attribute of pharmaceutical products and therefore, stability testing plays a crucial role in the drug development process.

Challenges in Early Phase Stability

Availability of stability-indicating methods: A significant challenge in the stability program of drug product during CMC drug development.

Limited knowledge of degradation pathways: pathways can be complex & involve intermediates formed during degradation. These intermediates may have unique physicochemical properties.

Developing stability-indicating analytical methods to accurately identify and quantify degradation products is a significant challenge.

"Phase appropriate" analytical method validation: Where do we draw the line. We need to show that our methods are stability indicating.

Summary

- Stability Studies provide evidence on how the quality of a manufactured DS or DP varies with time under the influence of a variety of environmental factors such as temperature, humidity and light.
- Stability programs enable recommended storage conditions, re-test periods and shelf lives to be established
- In addition, well-programs assist in product development determining properties of the product and meet appropriate regulatory requirements.
- Early phase programs face challenges around the availability and suitability of stability indicating analytical methods.

Thank you

Session VI: Quality Control & Stability Testing for Investigative Medicinal Product (IMP) and Registered Drugs

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